

## Digestive Sciences IRG

### OVERALL DESCRIPTION

The Digestive Sciences IRG will review applications on basic and clinical aspects of gastrointestinal, hepatobiliary and pancreatic physiology and pathobiology, and on the disposition and action of nutrients and xenobiotics. Specific areas include mucosal immunity and immune-mediated disorders, microbial pathogenesis, inflammation, and molecular and cell biology of pre-cancer, differentiation, growth and development. Applications involving integrative physiology including brain-gut interactions, hormones, secretion and absorption, motility, and genetic determinants of GI diseases will be reviewed here, as well as studies related to the disposition of nutrients, drugs, biopharmaceutical agents, alcohol and other toxicants, and their mechanisms of action. Investigators may employ a broad range of basic and clinical research methods including pharmacologic, chemical and biochemical approaches, genetics, genomics and proteomics, molecular and cell biology techniques and animal models. Patient-oriented studies including pediatric gastroenterology are included in this IRG, but large population studies and randomized clinical trials involving digestive disorders will be reviewed elsewhere.

Study sections in the IRG include:

- Xenobiotic and Nutrient Disposition and Action Study Section (XNDA)
- Gastrointestinal Cell and Molecular Biology Study Section (GCMB)
- Gastrointestinal Mucosal Pathobiology Study Section (GMP)
- Hepatobiliary Pathophysiology Study Section (HBPP)
- Clinical and Integrative Gastrointestinal Pathobiology Study Section (CIGP)

NOTE: Some of the Teams that will develop recommendations for other IRGs that may share interests in areas of research with the DIG IRG have not yet met or completed their deliberations. Therefore, the proposed “shared interest” guidelines for each of the study sections listed below are tentative, pending further input from the remaining study section design Teams, the community, and the CSR Advisory Committee to the Director, CSR.

### **Xenobiotic and Nutrient Disposition and Action (XNDA) Study Section**

The Xenobiotic and Nutrient Disposition and Action (XNDA) Study Section reviews applications related to the disposition (absorption, metabolism, distribution, and excretion) of supraphysiologic levels of (SP) nutrients and non-nutrient chemicals, including xenobiotics such as pro-drugs and drugs, biopharmaceutical agents, alcohol, phytochemicals/ botanicals, and other non-drug chemicals, and the study of their mechanisms of action (both pharmacological and toxicological) in normal and pathological conditions of the digestive system.

Studies that address the effects of digestive system-generated metabolites of xenobiotics on organ systems other than the digestive system may be considered in this

Study Section. XNDA may also lend its expertise to the review of applications that address the metabolism, disposition of xenobiotic in other organs (e.g., lung, immune system, reproductive system, kidney).

#### Specific Areas Covered by XNDA

- Gastrointestinal (including splenic/lymphatic) and/or hepatic disposition of SP nutrients (e.g., vitamins, minerals, amino acids, at supra-physiological levels), drugs (ranging from small molecules to biopharmaceuticals/macromolecules) and non-drug chemicals (including alcohol, metals, toxins, phytochemicals/botanicals and environmental toxicants), including processes of absorption, biotransformation, distribution and excretion.
- In vitro and animal models that study xenobiotic disposition.
- Biotransformation including the phase I (e.g., oxidation), phase II (e.g., conjugation) and phase III (e.g., transport) processes.
- Membrane processes related to xenobiotic and nutrient disposition, including passive, vesicular, receptor, and transporter-mediated processes (e.g., nutrient transporters, efflux transporters, MDR / MRPs, ion transport/channels).
- Hepatic clearance processes as related to xenobiotics and SP nutrients, including perfusion, uptake, binding, biotransformation, and/or biliary excretion.
- The role of bile acids and lipids in xenobiotic disposition and/or toxicity.
- Interactions among xenobiotics (e.g., drug-drug interactions, and nutrient-drug interactions, alcohol-drug interactions), involving disposition and response processes.
- Role of genetics and genomics in disposition and effects of SP nutrients and xenobiotics (e.g., pharmacogenetics, pharmacogenomics, toxicogenetics, toxicogenomics).
- In vitro and animal models that investigate the molecular basis of 'gene-environment' interactions related to the digestive system, including studies focused on putative environmental susceptibility genes and/or pharmacogenetics.
- Role of physiological variation in disposition and action of xenobiotics and SP nutrients.
- Theoretical, mechanistic, and/or integrated studies of kinetics and/or dynamics of SP nutrients and xenobiotics (e.g., pharmacokinetics, pharmacodynamics, toxicokinetics and toxicodynamics).
- Mechanisms of action of xenobiotics and SP nutrients, including toxicological and/or pharmacological effects on the digestive system.
- Xenobiotic and SP nutrient-mediated alterations in signal transduction, cell cycle regulation, receptors, genes, apoptosis and/or oncosis (necrosis).
- Structure-function relationships for enzymes/transporters/receptors involved in SP nutrient and/or xenobiotic disposition and effects.
- Production, elimination and biological effects of reactive intermediates, including reactive oxygen species (e.g., oxidative stress), mediated by SP nutrients or xenobiotics.

#### Shared Interests Within the DIG IRG

- Gastrointestinal Cell and Molecular Biology (GCMB): Where an application focuses on understanding fundamental processes/ pathways of dysplasia,

neoplasia, mutagenesis and/or DNA repair, it could be assigned to GCMB. Where the focus is on understanding the disposition and/or mechanisms of action of xenobiotics, or SP nutrients, the application could be assigned to XNDA.

- Gastrointestinal Cell and Molecular Biology (GCMB); Hepatobiliary Pathophysiology (HBPP); and Gastrointestinal Mucosal Pathobiology (GMP): There is shared interest in the area of oxidative stress with GCMB, HBPP and GMP. Where the focus of the application is to evaluate the toxicological or pharmacological implications of xenobiotic-induced oxidative stress (production/elimination of reactive intermediates, including reactive oxygen and nitrogen), it could be assigned to XNDA. Where the focus is on oxidative stress related to infection or inflammation, it could be assigned to GMP; where the focus is on the molecular and cellular processes that address endogenously-mediated oxidative stress, it could be assigned to GCMB. Where the focus is on oxidative stress related to ischemia-reperfusion injury or other mechanisms of hepatic cell injury, it could be assigned to HBPP.
- Hepatobiliary Pathophysiology (HBPP): (1) There is shared interest with HBPP in the area of biliary excretion. Where the focus is on understanding the physiological aspects of biliary function, the application could be assigned to HBPP. Where the focus is on biliary elimination of xenobiotics, or alterations of xenobiotic disposition by the hepatobiliary system, the application could be assigned to XNDA. (2) There is shared interest in the area of alcohol metabolism and effects between HBPP and XNDA. Where the focus of the application is on the disposition of alcohol, or the effects of alcohol on the disposition of other xenobiotics, the application could be assigned to XNDA. Where the focus is on the pathophysiology of alcohol-related liver disease the application could be assigned to HBPP.
- Clinical and Integrative Gastrointestinal Pathobiology (CIGP): (1) There is shared interest with CIGP in the area of gastrointestinal motility. Applications with a focus on understanding the consequences of altered GI motility on xenobiotic disposition (absorption) could be assigned to XNDA. All other studies related to GI motility could be assigned to CIGP. (2) There is shared interest with CIGP in the area of 'gene-environment' interactions. Laboratory-based studies examining pathways involved in 'gene-environment' interactions, including in vitro and animal models could be assigned to XNDA. Gene-environment interaction studies focused on human populations (epidemiologic or patient based) could be assigned to CIGP. Studies related to interactions of the microenvironment of the intestine and genes could be assigned to CIGP. (3) There is shared interest in the area of alcohol metabolism and effects between CIGP and XNDA. Where the focus of the application is on the disposition of alcohol, or the effects of alcohol on the disposition of other xenobiotics, the application could be assigned to XNDA. Where the focus is on the pathophysiology of alcohol-related pancreatic or intestinal disorders, the application could be assigned to CIGP.

#### Shared Interests Outside of the DIG IRG

- Biological Chemistry and Macromolecular Biophysics (BCMB) IRG: Shared interest exists for structure-function relationships for enzymes/transporters/receptors involved in nutrient and/or xenobiotic disposition. Where interests are focused primarily on structure-function relationship of enzymes, transporters and/or receptors for xenobiotics and nutrients in the digestive system, they could be assigned to the XNDA. Studies designed to address general principles of enzymes, transporters and/or receptors may be considered under the auspices of the BCMB IRG. Shared interests also exist in the study of pro-drugs. Studies focused primarily on the disposition and action of the pro-drug in the digestive system could be assigned to XNDA. In general, studies of pro-drug structure and function that use primarily biophysical techniques (e.g., X-ray diffraction, electron spin resonance, and single molecular techniques) could be assigned to the BCMB IRG.
- Bioengineering Sciences and Technologies (BST) IRG: Shared interests exist for mathematical modeling. Studies focused on mechanisms and applications in xenobiotic or nutrient (at supraphysiological levels) transport, pharmacokinetics, pharmacodynamics and toxicodynamics could be assigned to XNDA. Studies focused on developing mathematical modeling methods could be assigned to the BST IRG. Applications focused on GI specific biological mechanisms and therapies could be assigned to XNDA. Applications focused on developing technologies to introduce genes and drugs in a general cellular context could be assigned to the BST IRG.
- Immunological Sciences (IMM) IRG: There is shared interest with IMM in studies involving xenobiotics used to diagnose or treat immunological disorders and diseases. Studies on the mechanisms of action or efficacy of pharmaceutical agents used in the diagnosis or treatment of immune disorders or diseases may be appropriate for IMM. Similar studies of the use or action of immunological adjuvants may also be appropriate for IMM. Applications where the primary focus is on the disposition (absorption, metabolism, distribution, and excretion) of xenobiotics, including pharmaceutical agents may be appropriate for the DIG IRG.
- Infectious Diseases and Microbiology (IDM) IRG: When the emphasis is on the evaluation of the therapeutic mechanisms of action of novel agents that are potentially useful against infectious diseases, assignment to the IDM IRG may be appropriate. Applications where the primary focus is on the disposition (absorption, metabolism, distribution, and excretion) of xenobiotics, including pharmaceutical agents, or their toxicological effects on the host, may be appropriate for the DIG IRG.
- Oncological Sciences (ONC) IRG: Shared interests exist in the area of drug/biopharmaceutical development for cancer treatment including chemotherapy. When the emphasis is on the development and testing of cancer therapeutics, ONC IRG is appropriate. However, XNDA should be considered for applications related to GI toxicity of cancer therapeutics.
- Cardiovascular Sciences (CVS) IRG: Studies that examine arrhythmias due to administration of therapeutic agents may be assigned to the CVS IRG.

Applications that focus on the general disposition of pro-drugs and drugs or biopharmaceutical agents, and their mechanisms of action may be assigned to XNDA.

- Endocrinology, Metabolism, Nutrition and Reproductive Sciences (EMNR) IRG: Shared interests exist in areas of xenobiotic and/or nutrient metabolism, and toxicology. Studies could be assigned to XNDA when the kinetics and mechanism pertain to xenobiotics and nutrients utilized at therapeutic and/or toxicological doses. On the other hand, applications dealing with metabolic aspects of nutrients or food components, once absorbed and available to non-digestive system tissues and cells, could be assigned to the EMNR IRG. Basic or clinical studies that place a major emphasis on nutrients, xenobiotics, and endocrine disruptors and their action with endocrine systems may be assigned to the EMNR IRG. However, when interactions with the endocrine system are not the primary focus, assignment should be made to XNDA.
- Respiratory Sciences (RES) IRG: Shared interests exist in areas such as the disposition and action of drugs and other foreign materials when taken into the body. Studies could be directed to XNDA when they address the effects of digestive system-generated metabolites of xenobiotics or the absorption and excretion of xenobiotics by the digestive system or where multiple organ systems are involved or where the hepatic and /or gastrointestinal activities dominate. Applications that address the metabolism and disposition of xenobiotics in the lung may be assigned to the RES IRG. Environmental and occupational lung diseases (including interstitial lung diseases and asthma induced by environmental agents) and inhalation and respiratory toxicology, including the effects of particles and gasses, including drugs, on lung cells, may also be assigned to the RES IRG.
- Renal and Urological Sciences (RUS) IRG: Shared interests exist in areas such as renal transport mechanisms and drug therapy. Studies could be assigned to XNDA when the kinetics, dynamics and mechanisms address disposition and effects of drugs where multiple organ systems are involved, or where the hepatic and/or gastrointestinal activities dominate. Pharmacology relating to kidney function and toxic injury to the kidney: including xenobiotic-mediated alterations in renal signal transduction, cell-cycle regulation, receptors, genes, and apoptosis; as well as mechanisms of renal apoptosis and necrosis, senescence, genotoxic responses, DNA damage, oxidative stress, and cellular aging could be assigned to the RUS IRG.
- Surgical Sciences, Biomedical Imaging and Bioengineering (SBIB) IRG: Studies of the pharmacodynamics and pharmacokinetics, including toxicology, of general or local anesthetic agents may be assigned to SBIB. Studies of bioengineering approaches to facilitate drug delivery and studies of the use of biomaterials to modify drug delivery should be considered for assignment to SBIB. General studies of the disposition of xenobiotics, biopharmaceutical agents, phytochemicals/ botanicals, and other non-drug chemicals, and the study of their mechanisms of action, particularly when they relate to normal and pathological conditions of the digestive system, may be assigned to XNDA.

- Integrative, Functional and Cognitive Neurosciences (IFCN) IRG: Shared interests exist in areas where the pharmacological and/or toxicological effects of xenobiotics, including alcohol, on the nervous system are studied. Where studies relate primarily to the disposition of such xenobiotics, or toxicity to the digestive system, they could be assigned to XNDA. Where studies of xenobiotics relate primarily to effects on the nervous system, they could be assigned to the IFCN IRG.

## **Gastrointestinal Cell and Molecular Biology (GCMB) Study Section**

The Gastrointestinal Cell and Molecular Biology (GCMB) Study Section reviews applications concerning cell and molecular biology of gastrointestinal and liver function. Studies using cellular, molecular, genetic, structural, biochemical, electrophysiological and pharmacological approaches to define mechanisms and pathways of GI and liver growth, differentiation, development, physiology and pathophysiology in humans or model organisms generally at the level of the gene, protein or cell are considered.

### Specific Areas Covered by GCMB

- Regulation of gene expression including transcriptional and posttranscriptional mechanisms: transcription factors, promoter analyses, DNA-protein interaction, protein-protein interaction, chromatin structure and remodeling, epigenetic phenomenon, nuclear transport including import and export, mRNA processing including splicing and editing, covalent posttranscriptional control of gene expression including splicing, polyadenylation, mRNA stability, mRNA editing and translational control, genomics and proteomics.
- Mechanisms controlling growth, differentiation and development: origin, commitment, specification and differentiation of all cell types in the digestive system; cell-cell cell-tissue and tissue-tissue interactions that regulate organ development; inductive mechanism of tissue and organ development; lineage determination; pattern formation; cell cycle and cell division including cyclins, cyclin-dependent kinases and cyclin inhibitors; checkpoints; growth factors, mitogens, morphogens and cytokines.
- Signal transduction: receptor-ligand interactions; receptor-mediated gene regulation and signal pathways; intracellular signaling pathways in response to endogenous and exogenous stimuli; paracrine and autocrine signaling; second messengers; adaptor proteins; kinases; phosphatases; signaling involving cell cycle regulation and apoptosis; regulation by reactive oxygen species and nitric oxide.
- Intracellular trafficking: endocytosis; receptor and ligand internalization and recycling; intracellular compartmentalization; protein sorting; vesicular fusion, trafficking and docking; ER translocation; molecular chaperones; proteosomes.
- Gene and somatic cell therapy: viral-, liposome- and DNA-mediated gene transfer and delivery, somatic cell transplantation, tissue engineering, antisense RNA, RNA interference, transgenic mouse.
- Stem cell biology as relates to the digestive system including differentiation of embryonic and adult stem cells into the gastrointestinal epithelium and smooth muscle cells, hepatocytes and cholangiocytes.

- Mechanisms of apoptosis, cell cycle arrest and senescence: telomere biology, genotoxic responses, DNA damage, death receptors and ligands, oxidative stress, cellular aging.
- Molecular physiology of ion channels, pumps and transporters of water, electrolytes, and organic solutes: vectorial secretion and absorption, membrane potential, water channel, cell volume control, structural-functional analysis, protein-protein interaction.
- Molecular mechanisms of GI and liver secretion or absorption: vesicle formation, membrane trafficking, polarity determination, tight junction regulation, and scaffolding.
- GI and liver dysplasia and pre-neoplasia: mechanisms of transformation, immortalization and mutagenesis, DNA damage and repair, epigenetics, angiogenesis in relation to regeneration, imprinting, genomic and chromosomal instability, molecular screening, detection and diagnosis, mechanisms of hereditary syndromes.
- Genetic basis of GI diseases: structure-function analysis of identified disease-causing genes, genotype-phenotype correlation, and transgenic mouse model of hereditary human diseases.
- Epithelial repair, regeneration and adaptation: molecular mechanisms of liver regeneration in response to hepatectomy and injuries, gut adaptation in response to resection, nutritional depletion and other injuries; intestinal epithelial restitution and wound healing following injuries.
- Extracellular matrix (ECM) and cell-cell interaction: cell adhesion, migration, cell-cell communication, gap junction, endoderm-mesoderm interaction during development.
- Epithelial cell biology and barrier function: basal lamina formation, cytoskeleton, motor and motility, cell polarity determination, tight junction formation and regulation, cell-cell communication, permeability. Mechanics, biomechanics and cellular basis including the contractile proteins and crossbridge cycling in GI smooth muscle.

#### Shared Interests Within the DIG IRG

- Xenobiotic and Nutrient Disposition and Action (XNDA): Studies that address the effect of drugs or xenobiotics on cellular and molecular function, or the cellular and molecular effects on drug disposition should be assigned to XNDA.
- Gastrointestinal Mucosal Pathobiology (GMP): Shared interests exist between Gastrointestinal Mucosal Pathobiology (GMP) and GCMB with regards to GI pre-neoplasia and genetic basis of GI diseases. Whereas studies of pre-neoplasia, genetic causes and changes in epithelial cell biology and barrier functions due to inflammatory bowel disease or other inflammatory or infectious conditions of the lower digestive tract could be assigned to GMP, those involving characterization of disease-causing genes other than inflammatory bowel disease could be assigned to GCMB.
- Hepatobiliary Pathophysiology (HBPP): Shared interests exist between HBPP and GCMB in the areas of stem cell biology, cell transplantation and liver regeneration. Where studies that concern these areas at the organ level (i.e. liver) are assigned to HBPP, those that address these processes at a molecular

level should be assigned to GCMB. In addition, studies that examine signal transduction, intracellular trafficking, cell matrix, cell-cell interaction, ion channels and transporters in the liver could be assigned to HBPP.

- Clinical and Integrative Gastrointestinal Pathobiology (CIGP): In general, whereas studies concerning the use of molecular and cell biological techniques to address digestive functions except the pancreas should be assigned to GCMB, those involving an integrated approach should be addressed by CIGP. In genetic basis of diseases, CIGP will be assigned studies involving identification of disease-causing genes including those involved in complex traits. GCMB will be assigned applications on the functional characterization of previously identified disease-causing genes from a cellular and molecular biologic perspective. In GI pre-neoplasia of the upper digestive tract, studies involving etiology, diagnosis and prevention of conditions, including the identification of the genetic changes involved, that are a direct result of acid-related injuries (Barrett's esophagus) and H. pylori infection (intestinal metaplasia) may be assigned to CIGP, where studies that address the functions of genes and the consequences of mutation in these genes in all GI pre-neoplastic tissues will be referred to GCMB.

#### Shared Interests Outside of the DIG IRG

- Biological Chemistry and Macromolecular Biophysics (BCMB) IRG and Molecular Approaches to Cell Function and Interactions (MACFI) IRG: The GCMB Study Section may be assigned applications as they relate to GI- or liver- specific cell function whereas applications dealing with general biochemical mechanisms of cell functions could be assigned toward BCMB or MACFI IRGs.
- Genes, Genomes & Genetics (GGG) IRG: The GCMB Study Section may be assigned applications as they relate to GI- or liver- specific gene transcription and gene expression, as well as functional determination of previously identified genes that cause diseases of the GI tract and liver. Studies of general mechanisms of gene regulation, quantitative genetics, genetic epidemiology and genetic analysis of complex traits, and genetically engineered animals with an emphasis on genetics rather than digestive system diseases may be assigned to the GGG IRG.
- Biology of Development and Aging (BDA) IRG: In general, applications related to investigation of growth, differentiation, development, and stem cell biology of the gastrointestinal tract and liver at the molecular and cellular level would be assigned to GCMB. Similarly, applications that focus on early developmental mechanisms involved in formation of organ primordia (such as cell cycle control, apoptosis, cell fate, or early pattern formation) would be assigned to the BDA IRG. When the question being addressed is germane to the development of more than a single organ system, either because it addresses the "primordial organ" or because of the generality of the process being studied, the application generally would be assigned to the BDA IRG. The overall philosophy is that assignment should be made based on the central focus of the application.



- Bioengineering Sciences and Technologies (BST) IRG: Grant applications focused on GI specific biological mechanisms and therapies could be assigned to GCMB. On the other hand, grant applications focused on developing technologies to introduce genes and drugs in a general cellular context could be assigned to the BST IRG.
- Oncological Sciences (ONC) IRG: In general, studies of the biology, genetics, interactions of cells with their microenvironment, or biomarkers for early detection of GI dysplasia, pre-neoplastic conditions and pre-neoplastic conditions of the liver would be assigned to GCMB. Those that involve GI and liver cancers (invasive and metastatic cancers) and all other cancers including chemo- and radiation therapy would be assigned to the ONC IRG. Studies of familial adenomatous polyposis (FAP) as well as the pathology and treatment of polyps in the GI system would be assigned to GCMB. In general, cell biological studies of GI or liver cancers would also be assigned to the ONC IRG. Molecular and genetic studies of Barrett's Esophagus would be assigned to GCMB.
- Endocrinology, Metabolism, Nutrition, and Reproductive Sciences (EMNR) IRG: Shared interests exist with EMNR IRG regarding hormone physiology and biochemistry, and nutrient metabolism. In general, studies involving hormones and hormone receptors that originate from the gastrointestinal tract, and digestion and absorption of nutrients by the digestive system would be assigned to GCMB, whereas signal transduction studies involving hormones of endocrine system origin would be assigned to the EMNR IRG.

## **Gastrointestinal Mucosal Pathobiology (GMP) Study Section**

The Gastrointestinal Mucosal Pathobiology (GMP) Study Section reviews applications involving gastrointestinal immunology, host-microbial interactions, intestinal infections and inflammation including chronic inflammatory bowel disease. The intestinal epithelium is the interface between the intestinal immune system and the microbiota; thus epithelial cell biology as it relates to mucosal defense or repair is also included.

### Specific Areas Covered by GMP

- Gastrointestinal mucosal immunology including but not limited to studies on gut associated lymphoid tissue (GALT), intraepithelial lymphocytes (IEL), lamina propria lymphocytes (LPL), and draining mesenteric lymph nodes.
- Gastrointestinal responses to bacterial and dietary antigens including active immunity or tolerance, and the role of mucosal adjuvants in triggering either pathway.
- Mechanisms of innate immunity in host defense in the gastrointestinal system, including cryptins, defensins, lysozyme, mucins, and natural IgA decoy receptors.
- Mucosal immune and inflammatory responses to H. pylori infection
- Mucosal receptors for pathogens (including toxin) and for molecular pattern recognition (toll-receptors, and like receptors, NOD2)
- Mechanisms of acute and chronic intestinal inflammation in experimental models including studies on genetic susceptibility as they relate to pathogenesis.

- Basic and clinical studies in human inflammatory bowel disease, gluten sensitive enteropathy, auto-immune gastritis, and other types of immune-mediated gastrointestinal diseases.
- Identification of microbes/microbial products that drive chronic intestinal inflammation.
- Mechanisms of tissue injury and repair in intestinal inflammation.
- Interactions between the microbiota and intestinal mucosal including the effects of probiotics.
- Gastrointestinal cell biology and barrier function including cytokine and chemokine production in response to pathogens, toxins or chemical injury.
- Intestinal responses to enteric pathogens including enterocyte and immune responses.
- Host cell responses (including inflammatory mechanisms) to invasion by microbial pathogens in the gastrointestinal system.
- Gastrointestinal responses to food-borne infections, including toxin-mediated and invasive pathogens, and agents likely to be employed in bioterrorism
- Oxidant-induced injury including ischemia-reperfusion injury, neutrophil activation and endothelial cell responses
- Studies of GI tract related to dysplasia and pre-neoplasia as a consequence of chronic GI infection or inflammation, including familial adenomatous polyposis (FAP), and mechanisms of hereditary syndromes.
- NSAID-induced gastrointestinal injury and inflammation.
- Effects of alcohol or other toxicants on the gastrointestinal immune system.

#### Shared Interests Within the DIG IRG

There are shared interests in signal transduction, oxidative stress epithelial biology and barrier, and genetic basis of disease with other study sections in the IRG. Assignments to GMP will be based on a central focus on immunity, infection or inflammation of the gastrointestinal tract.

- Gastrointestinal Cell and Molecular Biology (GCMB): Applications with a focus on transcription factors such as NF-kappaB in animal models or humans with inflammation or infection could be assigned to GMP, while studies of transcription factors and gene regulation without such a focus will be assigned to GCMB. Studies on dysplasia and pre-neoplasia as a consequence of chronic gastrointestinal infection or inflammation will be assigned to GMP. All other studies in this area will be assigned to GCMB. Molecular and genetic studies of Barrett's esophagus would be assigned to GCMB.
- Hepatobiliary Biology and Pathobiology (HBPP): Studies regarding hepatic infection, inflammation or immune responses are appropriate for assignment to HBPP.
- Clinical and Integrative Gastrointestinal Pathobiology (CIGP): CIGP will be assigned studies regarding genetic susceptibility to IBD in humans. Studies involving functional analysis of genes associated with the pathogenesis of IBD or other gastrointestinal inflammatory states will be assigned to GMP. Patient oriented GI research would be assigned to CIGP. Studies on pancreatitis will be assigned to CIGP.

Shared Interests Outside of the DIG IRG

- Risk, Prevention and Health Behavior (RPHB) IRG: Applications that focus on physiologic or biologic processes of gastrointestinal disorders could be referred to GMP; if the primary focus is on psychological, behavioral or social-risk factors as well as clinical trials of behavioral medicine and lifestyle-based gastrointestinal prevention strategies and therapies could be referred to RPHB.
- Immunology (IMM) IRG: There are several shared interests between GMP and the IMM IRG in the area of mucosal immunology and inflammation. Typically, studies of general mucosal immunology, where the focus is on the immune system, would be assigned to the Immunology IRG. Similarly, studies on inflammatory bowel disease, gluten sensitive enteropathy, and other types of immune-mediated gastrointestinal diseases, where the focus is on the gastrointestinal system or liver, would be assigned to GMP.
- Infectious Diseases and Microbiology (IDM) IRG: Assignment to GMP may be appropriate for applications where the focus is on the mucosal-based inflammatory responses to pathogenic microbes and their products. Assignment to the IDM IRG may be appropriate for studies where the focus is the pathogen, or antibiotic therapy.
- Oncological Sciences (ONC) IRG: In general, studies of GI dysplasia, and pre-neoplastic conditions of the GI system or liver would be assigned to GCMB. Studies of familial adenomatous polyposis (FAP) as well as the pathology and treatment of polyps in the GI system would be assigned to GMP. Studies that focus on GI or liver cancers would be assigned to the ONC IRG.

**Hepatobiliary Pathophysiology (HBPP) Study Section**

This study section reviews applications involving alcohol metabolism and disease; cholesterol and bile salt metabolism; fibrosis and cirrhosis; liver immunology and inflammation; hepatobiliary transporters and ion channels; mechanisms of cell death and inflammation; cell biology of liver cells; mechanisms of repair and regeneration; pathophysiology and treatment of inherited and acquired hepatobiliary diseases; viral hepatitis and liver transplantation.

Specific Areas Covered by HBPP

- Pathogenesis of alcoholic liver injury, including the role of nutrient deficiencies and endotoxemia.
- Mechanisms of hepatic cholesterol and lipid metabolism as it relates to bile formation.
- Bile salt synthesis, metabolism and transport.
- Mechanisms of bile formation and cholestasis.
- Effects of bile salts on lipid absorption/assembly and regulation of lipoprotein genes

- Physiologic mechanisms of hepatobiliary transport, including mechanisms of uptake and excretion of organic solutes, heavy metals, and ions.
- The use of isolated parenchymal and non-parenchymal cells of the liver including hepatocytes, stellate cells, Kupffer cells, endothelial cells, cholangiocytes and resident lymphocytes particularly as they relate to the pathogenesis of liver disease.
- Pathogenesis and treatment of autoimmune, cholestatic, metabolic, viral mediated and non-alcoholic fatty liver diseases (NAFLD) and cholangiopathies.
- Pathogenesis of gallstones and gallbladder disease
- Cellular and molecular mechanisms of fibrosis and cirrhosis including complications such as ascites and hepatic encephalopathy.
- Mechanism of hepatocyte injury including immune response, oxidative stress, apoptosis, pro- and anti-inflammatory mediators, including signal transduction pathways and neuromediators.
- Inflammatory response of the liver to injury or infection (acute phase response).
- Studies of gene regulation as they pertain to the pathogenesis of liver diseases.
- Studies of liver organ repair and regeneration.
- Regulation of splanchnic blood flow as it pertains to mechanisms of portal hypertension.
- Liver cell and organ transplantation, liver ischemia-reperfusion injury, and application of transplantation to the therapy of liver diseases.
- Gene and progenitor cell therapy of genetic and acquired hepatobiliary diseases.
- Viral hepatitis as it relates to the pathogenesis of hepatobiliary disease.

#### Shared Interests Within The DIG IRG

- Xenobiotic and Nutrient Disposition and Action (XNDA): There is a shared interest with XNDA in alcohol metabolism and toxicity, hepatobiliary transporters, and cholesterol and lipid transport. Applications that focus on these processes in the physiology and pathophysiology of liver diseases could be assigned to HBPP. Studies focused on xenobiotics and nutrients should be referred to XNDA.
- Gastrointestinal Cell and Molecular Biology (GCMB): There is shared interest with GCMB in mechanisms of signal transduction, intracellular trafficking, cell-cell and cell-matrix interactions, gene regulation, gene and somatic cell therapy and progenitor cells, mechanisms of cell death and molecular physiology of ion channels and transporters, liver repair and regeneration. Applications that focus on these processes as they relate to liver diseases could be assigned to HBPP.
- Gastrointestinal Mucosal Pathobiology (GMP): There is shared interest with GMP in mechanism of inflammation. Studies regarding hepatic infection and inflammation should be assigned to HBPP.
- Clinical and Integrative Gastrointestinal Pathobiology (CIGP): There is also shared interest with CIGP with inherited metabolic disorders of the liver and patient oriented research. Studies that are focused on the pathogenesis of the inherited metabolic disorders of the liver and treatment of diseases could be

assigned to HBPP. In general patient oriented research on the liver would be assigned to CIGP.

Shared Interest Outside the DIG IRG:

- Genes, Genomes & Genetics (GGG) IRG: Applications that focus on gene transcription studies of the pathophysiology of liver disease could be assigned to the HBPP. When the focus is a general understanding of gene transcription, assignment could be to the GGG IRG.
- Molecular Approaches to Cell Function and Interactions (MACFI) IRG: Shared interest with membrane transport, apoptosis, intracellular trafficking and cytoskeleton, signal transduction, cell-junction and cell-cell matrix interaction. When the focus is on a general cellular and molecular understanding, assignment could be to the MACFI IRG. Applications dealing with hepatobiliary cells as related to pathobiology of liver disease could be assigned to the HBPP study section.
- Bioengineering Sciences and Technologies (BST) IRG: Applications focused on liver specific biological mechanisms and therapies could be assigned to HBPP. On the other hand, grant applications focused on developing technologies to introduce genes and drugs in a general cellular context could be assigned to the BST IRG.
- Immunology (IMM) IRG: Applications focusing on inflammation, innate immunology, and autoimmune diseases of liver might be assigned to HBPP. Liver transplant applications, where the focus is on transplant immunology, could be assigned to the IMM IRG, whereas those related to pathobiology of organ function could be assigned to HBPP. Applications on basic, pre-clinical, and clinical investigations involving the etiology, initiation, immunopathophysiology, prevention and treatment of diseases in which the immune system plays a major role, maybe assigned to the IMM IRG.
- Infectious Diseases and Microbiology (IDM) IRG: Shared interest with viral infections (including hepatitis). Applications dealing with the response to viral infections as it relates to the pathogenesis of liver injury could be assigned to the HBPP study section. Assignment to the IDM IRG may be appropriate for studies where the focus is on the virus.
- Hematology (HEM) IRG: Shared interest with iron metabolism and stem cell biology. Applications dealing primarily with liver complications of iron overload and hepatic progenitor cells could be assigned to HBPP while those dealing with iron and heme metabolism as related to blood disorders, iron overload states and strategies for therapeutic intervention and sideroblastic anemias, acquired and inherited could be assigned to the HEM IRG.
- Cardiovascular Sciences (CVS) IRG: Shared interest with cholesterol and lipid metabolism, cytokines and nitric oxide. Proposals dealing with lipid metabolism in the arterial wall or arterosclerosis could be assigned to the CVS IRG.

Applications on the biochemistry of elevated plasma lipids and lipoproteins in the intestine and liver may also be assigned to the CVS IRG when the focus is on atherosclerosis and inflammation in the cardiovascular system. Applications dealing with cholesterol and lipid metabolism as it relates to bile salt metabolism and excretion, and the role of cytokines and nitric oxide in the pathogenesis of liver diseases could be assigned to HBPP.

- Endocrinology, Metabolism, Nutrition, and Reproductive Sciences (EMNR) IRG: Shared interest with cholesterol metabolism and complications of diabetes. Applications dealing primarily with lipid metabolism in the liver as it relates to NAFLD could be assigned to the HBPP study section. On the other hand applications focusing on lipoproteins, lipid metabolism and diabetic complications could be assigned to the EMNR IRG.
- Surgical Sciences, Biomedical Imaging and Bioengineering (SBIB) IRG: Shared interest with transplantation and reperfusion injury. Applications dealing with liver transplantation and its functional complications, liver ischemia and reperfusion injury can be assigned to either the SBIB IRG or the HBPP study section depending on the available expertise in the review groups.

## **Clinical and Integrative Gastrointestinal Pathobiology (CIGP) Study Section**

The Clinical and Integrative Gastrointestinal Pathobiology (CIGP) study section will consider research applications concerned with basic and clinically oriented research related to GI motility, brain-gut interactions, the enteric nervous system, motor disorders, acid secretion and acid related disease, GI hormones, pancreatic function and dysfunction, digestive system nutrient absorption and disposition, digestive system malabsorption/malnutrition, nutritional support, integrative GI physiology, genetic determinants of digestive diseases, and digestive system patient-oriented research related to the GI system, pancreas and liver. Clinical research involving interventional and diagnostic endoscopy and surgery are also included here.

### Specific Areas Covered by GCIP

- GI motility: Integrative gut motility, secretion and absorption at whole animal, organ, cellular and molecular genetic levels. Muscular and neural mechanisms of and control of contraction and relaxation of gastrointestinal sphincters and non-sphincteric smooth muscle including functions of receptors, ligands, ion channels, hormones, neurotransmitters, intracellular signal transduction pathways, reflex control of GI motility, genetic control mechanisms of GI motility.
- Brain-gut interaction: This broad area includes extrinsic and intrinsic neural control of GI sensory/motor and secretory function, endocrine, circulation and gut immune systems, including intraluminal immunogens and microorganisms. The area also includes dynamics and reciprocal influence of brain-gut and gut-brain interaction including those of cerebrocortical, brainstem and brain sensory motor nuclei.
- Enteric nervous system: Gastrointestinal sensory pathways and functions in health and disease. These include mechanisms, electrophysiology signal

- transduction of visceral nociceptors and nociceptive pathways originating in the viscera to the various levels of the CNS and to the cerebral cortex. It also includes studies of the mechanisms of visceral hypersensitivity, allodynia, and chronic visceral pain.
- Motor disorders: Pathophysiology of motor abnormalities in animal models or humans including the disorder that are congenital, developmental, or related to aging, inflammation, and use of a toxin. Physiology and pathophysiology of motor disorders of pharynx, esophagus, stomach, small and large bowel and the anorectum including swallowing disorders, gastroparesis, intestinal pseudoobstruction, paralytic ileus, constipation and fecal incontinence.
  - Acid secretion and acid related disease: Gastroesophageal reflux disease and gastrointestinal damage due to gastrointestinal secretions associated with reflux or misdirection of gastrointestinal secretions. Studies of supra-esophageal complications of GERD and of esophageal intestinal metaplasia and adenocarcinoma (Barrett's esophagus) are included. Functional consequences of *Helicobacter pylori* in the gastrointestinal system. Physiology, pathophysiology of treatment of peptic ulcer, gastritis and premalignant lesions of the gastric mucosa.
  - GI hormones: GI hormones, transmitters, and integrated function on target tissues. Brain-gut axis, endocrine cells of the GI tract, peptide transmitters and their actions.
  - Pancreatic function and dysfunction: Functional studies of the pancreas including neurohumoral regulation, pancreatic secretion, exocrine-endocrine relationships, and organ growth and development. Exocrine pancreatic diseases and dysfunction including both acute and chronic pancreatitis, cystic fibrosis and ischemia/reperfusion injury. Studies of gene and progenitor cell therapy for genetic and acquired pancreatic diseases and those dealing with pancreatic transplantation.
  - Digestive system nutrient absorption and disposition: Includes studies on the digestion, absorption, and gastrointestinal metabolism and disposition of nutrients when given at physiologic levels either as food or as supplements. Nutrients include macronutrients (fat, carbohydrate, protein) and micronutrients (vitamins, minerals), phytochemicals and non-digestible dietary components. The development of animal and artificial models for studying the absorption and digestion of unique dietary components (e.g. phytochemicals) are included.
  - Digestive system malabsorption/malnutrition: Human and animal studies on malabsorption of macronutrients (fat, protein, and carbohydrate) and micronutrients (vitamins, mineral, other food components) by the digestive system. The effects of primary or resultant malnutrition on GI organ function such as digestion and non-drug absorptive processes, liver function, pancreatic function, gallbladder function and gut immunity are included.
  - Nutritional support: The metabolic and nonmetabolic complications on the digestive system of enteral and parenteral nutrition delivery across the lifespan. Gut adaptation and outcome research are included. Novel nutritional ingredients and their effects on GI organ function are included.
  - Integrative GI physiology: Human and animal studies ranging from normal physiology to mechanisms and consequences of disease are appropriate for review. Investigation may include salivary, oropharyngeal, esophageal, gastric, intestinal physiology, pathobiology and pharmacology including the neural and mesenteric circulatory systems as they relate to the gastrointestinal tract.

Studies of fluid and electrolyte transport, intraluminal digestion, diarrhea and constipation are included. Disease modifiers can include genetic predisposition, diet and environmental conditions.

- Genetic determinants of digestive diseases: Germ line DNA sequence variants associated with increased risk of disorders of the digestive tract including syndromes, familial disorders, inherited metabolic disorders of the liver, gene-gene interactions, genetic risk assessment, gene-environment interactions including smoking, alcohol, diet, chronic inflammation and other environmental exposures. Gene knock-out and transgenic animals related to these diseases.
- Patient oriented research: Studies of risk factors, etiology, detection, screening, modifying factors and therapy of selected digestive system diseases and disorders including functional gastrointestinal, pancreas and liver disorders. Functional consequences of behavioral disorders including non-cardiac chest pain and irritable bowel syndrome are included. This includes pediatrics.
- Surgery: Clinical, population or integrative, whole animal studies of the responses of the digestive system to trauma or surgery and digestive system ischemia/reperfusion injury.

#### Shared Interests Within the DIG IRG

- Xenobiotic and Nutrient Disposition and Action (XNDA): The XNDA study section will deal with nutrients, phytochemicals and botanicals when presented at supra-physiologic and pharmacologic doses (used as drugs) and the CIGP study section will deal with nutrients as presented in the diet or supplements at physiologic levels. The XNDA will deal with toxicologic or pharmacologic effects and disposition of nutrients and the CIGP will deal with physiologic effects of nutrients. There is a shared interest with XNDA in alcohol metabolism and toxicity. Applications that focus on these processes in the physiology and pathophysiology of pancreatic diseases could be assigned to CIGP. Studies focused on xenobiotics and nutrients should be referred to XNDA.
- Gastrointestinal Cell and Molecular Biology (GCMB): In general, whereas studies involving an integrated approach should be addressed by CIGP, those concerning the use of molecular and cell biological techniques to address digestive functions, except the pancreas, should be assigned to GCMB. Signal transduction and cell-cell interactions as they relate to gastrointestinal physiology, neurotransmission, and motility are appropriate for assignment to the CIGP study section. Molecular and genetic studies in all GI neoplasias and dysplasias including Barrett's esophagus, intestinal metaplasia and colonic pre-neoplasia should be considered by GCMB. Integrative and clinical studies of Barrett's esophagus and pre-neoplastic conditions of the stomach and esophagus will be considered by CIGP. Studies of diagnosis, early detection, endoscopy, and prevention could be assigned to CIGP. In pancreatic studies, those that utilize molecular and cellular approaches to understand pancreatic physiology, as well as those focused on the basic processes of pancreatic physiology that are relevant to other digestive organs should be assigned to CIGP.
- Gastrointestinal Mucosal Pathobiology (GMP): H. pylori immunology, inflammation and host response, host-microbial interaction, and animal models



examining immune response, would be appropriate for assignment to GMP. H. pylori related to ulcer pathogenesis, gastric pathobiology, treatment, prevention, relapse will be dealt with CIGP. GMP will deal with mouse genetics and animal models as they relate to immunology of inflammatory bowel disease. Human statistical approaches, human genetics, and studies of gene-environment or gene-therapy interactions are appropriate for assignment to CIGP. Studies on pancreatitis will be assigned to CIGP.

- Hepatobiliary Pathophysiology (HBPP): Studies of the regulation of splanchnic blood flow related to portal hypertension and its consequences would be assigned to HBPP whereas studies of the circulatory system related to the remainder of the GI tract will be assigned to CIGP. There is also shared interest with CIGP with inherited metabolic disorders of the liver and patient oriented research. Studies that are focused on the pathogenesis of the inherited metabolic disorders of the liver and treatment of liver diseases could be assigned to HBPP. In general patient oriented research on the liver would be assigned to CIGP.

#### Shared Interests Outside of the DIG IRG

- Genes, Genomes & Genetics (GGG) IRG: In general, studies of genetics, genomics and related aspects of population dynamics would be assigned to CIGP when the gastrointestinal system is the primary focus of the research. Similarly, gene mapping, gene discovery, statistical analysis of simple and complex traits, and genetic epidemiology would be appropriate for the GGG IRG.
- Biology of Development and Aging (BDA) IRG: Studies of early developmental biology may be assigned to the BDA IRG. When the focus is the development of motility in lineages already committed to formation of smooth muscle GI elements, assignment may be to CIGP. When GI motor disorders are a secondary aspect or a part of a multi-system study of the aging process, assignment could be appropriate for BDA IRG; when GI motor disorders are the primary study focus, whether they are the result of developmental abnormalities, congenital disorders or aging, the assignment could be to CIGP.
- Bioengineering Sciences and Technologies (BST) IRG: Applications focused on gastrointestinal or pancreatic dysfunction and therapies may be assigned to CIGP. Applications focused on developing technologies to introduce genes and drugs in a general cellular context may be assigned to the BST IRG.
- Health of the Population (HOP) IRG: Applications in which the primary outcomes are population studies related to demographics or epidemiology may generally be assigned to the HOP IRG. Applications on the diseases, disorders, or functional consequences of behaviors could be assigned to CIGP.
- Oncological Sciences (ONC) IRG: Shared interests exist in the area of esophageal/intestinal metaplasia and adenocarcinoma. In general, cell biological studies of GI cancers would be assigned to the ONC IRG. However, studies involving etiology, diagnosis and prevention of conditions directly resulting from acid-related injuries (Barrett esophagus) and H. pylori infection (intestinal metaplasia) should be assigned to CIGP.

- Endocrinology, Metabolism, Nutrition, and Reproductive Sciences (EMNR) IRG: (1) Assignment could be made to CIGP when the focus of the application is on the digestion, absorption and GI, liver or pancreas metabolism of nutrient and non-nutrient components of the diet or supplements when presented at physiologic levels. Molecular aspects of nutrient transport and excretion, and disposition of nutrients once absorbed and their subsequent metabolism by organs or tissues other than those of the digestive system, could be assigned to the EMNR IRG. Studies of nutritional support in digestive/gastrointestinal diseases and disorders would in general be assigned to CIGP. Studies of the treatment of metabolic or hormonal disorders and diseases other than those of the digestive system, including the use of nutritional support, would in general be referred to the EMNR IRG. Studies of placental nutrient transport and the consequences for fetal growth may be assigned to the EMNR IRG. Dietary and physiological influences on the handling of nutrients by the gastrointestinal tract may be assigned to CIGP. (2) When the primary focus is on hormones of the gastrointestinal tract and peptides and neurotransmitters of the brain-gut axis, applications should be assigned to CIGP. Applications that focus on GI hormones that interact with pituitary, placental, or pancreatic hormones at the endocrine gland level, or on gut-mediated effects on feeding, satiety, energy expenditure and islet hormone secretion could be assigned to the EMNR IRG.
- Renal and Urological Sciences (RUS) IRG: CIGP may be assigned applications on the disposition of nutrient and non-nutrient components of the diet or supplements when presented at physiologic levels and when the disposition is primarily hepatic or gastrointestinal. Applications on the pathogenesis of proteinuria and clinical studies of the metabolic and nutritional consequences of the nephrotic syndrome could be assigned to the RUS IRG.
- Surgical Sciences, Biomedical Imaging and Bioengineering (SBIB) IRG: (1) Surgical interventions to treat digestive system dysfunctions may be assigned to the SBIB IRG. Patient oriented or whole animal research on the responses of the digestive system to trauma, surgery, or other physiologic stress may be assigned to CIGP. (2) Patient-oriented or whole animal studies of ischemia/reperfusion injury associated with surgery can be appropriately assigned either in the SBIB IRG or in CIGP, with CIGP focused more on cardiovascular evaluation of surgical or bypass procedures. (3) There is potential shared interest with the SBIB IRG in regard to nutritional support. CIGP may be assigned applications that relate to nutritional support in digestive system disease and disorders, whereas the SBIB IRG could be assigned applications that relate to nutrition support in surgery, burn, sepsis and trauma.
- Integrative, Functional and Cognitive Neuroscience (IFCN) IRG: In general, the CIGP study section would be assigned applications that focus on the enteric nervous system control of the gastrointestinal tract and pancreas. Similarly, applications focusing on mechanisms underlying general homeostasis and other integrative mechanisms and functions of the autonomic nervous systems would be assigned to the IFCN IRG.